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HOW COMMON IS ISOLATED NOCTURNAL HYPERTENSION?

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The growing use of methods to measure blood pressure (BP) under everyday life conditions in "out-of-office" settings, through either 24-hour ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM), for defining BP status has led to identification of four specific hypertension phenotypes, characterized by variable agreement or disagreement between office blood pressure (OBP) and out-of-office BP: true normotension (normal office and out-of-office BP), sustained hypertension (both elevated office and out-of-office BP), masked hypertension (normal office BP and out-of-office BP), and white-coat hypertension (WCH), when OBP is elevated but out-of-office BP levels are within normal limits [1-2]. The term 'white-coat hypertension' is probably a misnomer and a misconception, because it does not necessarily reflect, or at most partially, an alerting reaction or white-coat effect [3]. However, the suggestion to use the term "isolated office hypertension" instead of the more appealing "white coat hypertension" has not gained popularity in clinical practice [2].

The definitions of WCH and masked hypertension (MHT) originally applied to people who were not taking antihypertensive therapy. However, patients on antihypertensive therapy may also exhibit the same BP measurement pattern. It has been proposed to describe discrepancies between office and out-of-office BP in patients treated for hypertension, with the terms masked uncontrolled hypertension (MUCH) (office BP controlled but home or ambulatory BP elevated) and white-coat uncontrolled hypertension (WUCH) (office BP elevated but home or ambulatory BP controlled), compared with sustained or true uncontrolled hypertension (SUCH) (both office and home or ambulatory BP are uncontrolled) [1-2] .

Originally the definitions of WCH and MHT were based on clinic BP and awake or 24 h ambulatory BP, using ABPM as the method to assess out-of-office BP. More recently, in recognition of the prevailing prognostic value of night-time BP levels over other components of the 24-hour ABPM,

the ESH has recommended the incorporation of night-time BP into the definition of WCH and MHT [1-2].

Isolated nocturnal hypertension (INH) is another unique phenotype that could be identified by the ABPM, but not by clinic BP measurement. It is characterized by elevated night-time BP (>120 and/or 70 mmHg) in the presence of normal daytime BP [4]. When this condition is accompanied by clinic BP values in the normotensive range, INH may be considered a subtype of masked hypertension, that can be defined masked nocturnal hypertension, in untreated subjects or masked uncontrolled nocturnal hypertension, in patients treated with antihypertensive drugs [1, 4-5].

INH was first described in 2007 by Li et al. as novel clinical entity characterized by elevated night-time BP (>120 and/or 70 mmHg) in the presence of normal daytime BP (<135/85 mmHg). [4]. They examined a Chinese cohort of 677 participants enrolled in the JingNing population study and identified INH in 74 (10.9%) individuals. These subjects, compared to those with ambulatory normotension, were older, more often reported alcohol intake, had faster night-time pulse rate, had higher serum cholesterol and blood glucose levels [4].

Only 5.4% of the participants with INH had elevated clinic BP in this cohort study, highlighting the value of ABPM, which is the only mean by which a diagnosis of INH can be made [4]. It is therefore largely masked because of the limited use of ABPM. For this reason, it was called “a disease masked in the dark” [5].

The prevalence of INH was reported to be higher (20.4 %) in a population of 1282 patients with chronic kidney disease (CKD) admitted to a Chinese hospital division [6]. In this study INH was independently associated with age, estimated glomerular filtration rate and clinic diastolic BP.

The frequency and clinical characteristics of INH were recently investigated also in 198 Japanese children and young patients with CKD, where this condition was detected in 32 (16%) subjects [7].

A similar result (13.4%) was more recently obtained in the Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study, a cross-sectional multicenter cohort investigation conducted in nearly 700 European children with CKD.

In retrospective analyses of the International Database of the Ambulatory Blood Pressure (IDACO) [5], the prevalence of INH was higher among South Africans of black ancestry (10.2%) and Japanese (10.9%) than in Western (6.0%) and Eastern (7.9%) Europeans [5].

In a Swedish study, conducted by Wijkman et al. [9] in 414 middle-aged patients with type 2 diabetes, 30 (7.2%) subjects fulfilled clinic and ambulatory BP criteria for masked INH.

In the Jackson Heart Study, INH was found in about one fifth of the entire cohort (19%) [10]. Individuals with INH were characterized by older age, higher levels of total and LDL cholesterol, and higher prevalence of type 2 diabetes mellitus than counterparts with normal BP (19% versus 10%) [10].

Among the 2021 subjects enrolled in the Pressioni Monitorate E Loro Associazioni (PAMELA) study, representative for gender and age decades of the population of Monza in Italy, elevated night-time BP and normal awake BP was observed in 11.4% of the participants [11]. Persons with INH had many features of the metabolic syndrome, were older and more obese than the normotensive participants [11].

Data from the Spanish ABPM Registry showed that masked uncontrolled hypertension was very common (37%), most often because of poor control of nocturnal BP, with the proportion of patients in whom MUCH was solely attributable an elevated nocturnal BP almost double that solely attributable to daytime BP elevation (24.3 vs. 12.9%) [12].

The study of Salazar et al, published in the current issue of Journal of Hypertension adds a new piece of evidence in this scenario [13]. The aim this prospective cohort investigation conducted in Argentina, was to assess the prevalence of INH in 1344 patients referred to perform an ABPM for

diagnostic or therapeutic purposes. INH was detected in 12.9 % of the study population. Its prevalence was lower in subjects with office hypertension than in normotensive ones (7.4 vs. 17.2%, P<0.001) and similar between nonhypertensive office BP categories (optimal, normal and high-normal BP) [13]. Nocturnal hypertension was the more prevalent phenotype of masked hypertension and more than one-third of the individuals with nocturnal hypertension had INH. In multivariate analyses the independent correlates of INH were only age, waist and neck circumferences. It is important to note that the chance of having INH was unrelated to office BP categories [13]. This finding makes the identification of INH more difficult, being unrealistic to perform ABPM in all normotensive subjects.

Even if the findings of the current study contribute to expand our knowledge about INH, providing useful insights about this challenging BP phenotype, some weaknesses must be acknowledged when interpreting its results.

The sleep apnoea syndrome (SAS) is a well-known cause of nocturnal BP increase [2]. Therefore, the absence of polysomnographic data, as well as not having used validated questionnaires to screen for SAS, such as the Berlin Questionnaire, the STOP-Bang, or the Epworth Sleepiness Scale may be limitations of the current study.

The long- term and short-term reproducibility of INH has been reported to be poor, in the only two investigations exploring this issue [4,]. Unfortunately, this question could not be addressed in the study of Salazar et al, because participants completed only one ABPM.

Available evidence supports the association of INH with an increased risk of CV morbidity and mortality. In a multivariate adjusted analysis of the data from over 8000 participants from three continents in the IDACO database, INH was associated with a higher risk of all cardiovascular events (HR 1.38 [1.02–1.87]; *p* = 0.037) and total mortality (HR 1.29 [1.01–1.65], *p* = 0.045), as compared to nocturnal normotension [24] More recently, in a total of 588 Chinese CKD patients

multivariable Cox regression analyses showed that INH, even when adjusted for clinic BP, 24-hour BP, or daytime BP, was associated with an increased risk for renal events (hazard ratio [HR], 3.81; 95% CI, 1.74–8.36) and cardiovascular events (HR, 8.34; 95% CI, 1.98–35.07) compared with nocturnal normotension.

This enhanced risk may be mediated by an increased prevalence in subjects with INH of hypertension mediated organ damage (HMOD). However, the studies exploring the relationships between INH and HMOD yielded conflicting results (Table 1) [4-5, 8-11]. Controversy also exists on the question which blood pressure (BP) pattern – isolated daytime or nocturnal hypertension - has greater impact on HMOD. In this regard, the study of Salazar, cannot provide help, because information regarding target organ damage was not available . Therefore, additional research are needed to elucidate these important issues.

Moreover, future investigations should assess the better strategy to identify subjects with masked INH and whether or not targeting INH by planning a chronotherapeutic approach in prospective studies reduces cardiovascular events.

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Table 1. Studies exploring the prevalence of isolated nocturnal hypertension (INH) and of masked isolated nocturnal hypertension (MNH) and their relationships with some markers of target organ damage.

Authors, year [ref]	N. of subjects	Prevalence of INH (MNH) %	Markers of hypertension mediated organ damage in INH compared to normotension						
			PWV	AoAIx	Carotid IMT and plaques	Estimated GFR	Proteinuria	ECG-LVH	ECHO-LVH
Li Y et al, 2007 [4]	677	10.7 (13.2)	↑	=	NA	NA	NA	NA	NA
Wijkman M et al, 2009 [9]	414	(7.2)	↑	=	NA	=	NA	NA	=
Wang M et al, 2015 [6]	1282	20.4	NA	NA	↑	↓	NA	NA	NA
Cuspidi C et al, 2017 [11]	2021	11.4	NA	NA	NA	NA	NA	↑	↑
Fujita H et al, 2017 [7]	198	16 (8.1)	NA	NA	NA	NA	NA	NA	NA
Düzova A et al, 2019 [8]	688	13.4 (14.4)	↑		↑	NA	NA	NA	NA
Ogedegbe G et al, 2013 [10]	425	19.1	NA	NA	NA	NA	=	NA	=
Li Y et al (International Database of Ambulatory Blood Pressure Monitoring), 2007 [4]	6038	Overall: 7.7 South Africa (Black): 10.2 Japan: 10.9 Western Europe: 6 Eastern Europe: 7.9	NA	NA	NA	NA	NA	NA	NA
Salazar MR et al, 2019 [13]	1344	12.9 %	NA	NA	NA	NA	NA	NA	NA

↑ Increased in INH compared to true normotension; ↓ Reduced in INH compared to true normotension;
= No difference between INH and true normotension; NA: Not assessed;
PWV: pulse wave velocity; AoAix: Aortic Augmentation index; IMT: intima-media thickness; GFR: glomerular filtration rate;
ECG-LVH: Left ventricular hypertrophy diagnosed by Electrocardiogram; ECHO-LVH: Left ventricular hypertrophy diagnosed by Echocardiogram.